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Attorney Docket No. 55325-8148.US06

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
Martin & Zalipsky

APPLICATION NO.: 10/016,324

FILED: December 10, 2001

FOR: **THERAPEUTIC LIPOSOME COMPOSITION AND METHOD OF PREPARATION**

EXAMINER: Kishore

ART UNIT: 1615

CONF. NO: 4133

Transmittal of Reply Brief

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. Transmitted herewith are the following:

   ☒ Appellant's Reply Brief

   ☒ Two References

2. Conditional Petition for Extension of Time:

   Applicant petitions for an Extension of Time, if necessary, for timely submission of this transmittal and enclosures.

3. Provisional Fee Authorization

   No fees are believed due with this Reply Brief. However, the Commissioner is hereby authorized to charge any underpayment in fees for timely filing of this transmittal and enclosures to Deposit Account No. 50-2207.

Respectfully submitted,

Date: Feb. 27, 2004

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[55325-8148/BY040580.049]

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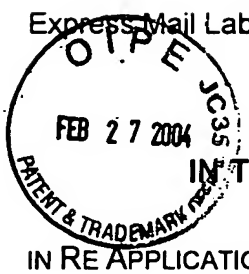
Attorney Docket No. 55325-8018.US06



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APPELLANT'S REPLY BRIEF

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a reply brief in response to the Examiner's Answer mailed December 30, 2003.

1. In the Examiner's Answer, the Examiner states that "the method of preparation as noted from Marshall's example 6 on col. 54 (lines 24-29) is a typical art known method of preparation of liposomes just as in the instant method" (page 3, lines 1-3 of Examiner's Answer).

In Example 6, Marshall prepares lipid-DNA complexes using the method referred to in the liposome art as the "thin-film hydration" method, where a dried lipid film is hydrated with an aqueous solution to form liposomes (see Szoka, F. and Papahadjopoulos, D., *Ann. Rev. Biophys. Bioeng.*, 9:467 (1980), page 480, first paragraph under "Preparation of Liposomes"). Indeed, this is a "typical art known method of preparation of liposomes" as the Examiner notes. Yet, the Examiner neglects to specify that this is a typical known method for preparation of liposomes that entrap small organic drug compounds where lipid-drug charge effects are minimal or absent (see Szoka and Papahadjopoulos, *supra*, pages

494-498). In Marshall *et al.*, the hydration medium includes negatively-charged DNA, which is uncommon in conventional liposome formulations. The liposome art has long recognized that encapsulation of DNA into liposomes is technically difficult, as supported by Wasan, E.K. *et al., J. of Pharmaceutical Sciences,* 85(4):427 (1996), copy enclosed (see page 427, Col. 2, lines 5-7). Thus, although the known thin-film hydration method may be used in Marshall *et al.*, formation of liposomes does not necessarily follow, due to the presence of charged species in the formulation.

2. On page 3, lines 3-7, the Examiner states that Appellant's arguments regarding aggregation are not persuasive since no literature evidence is submitted to show that liposomes are stable particles with little tendency to aggregate," and that "[t]he statement therefore, is deemed to be speculative in nature."

As evidence that this statement is not speculative, Appellant refers the Examiner to pages 500-501 of Szoka and Papahadjopoulos, *supra*, where the stability of liposomes is discussed. This articles states that liposome preparations can maintain their size, *i.e.,* do not aggregate, for periods of time.

3. On page 3, lines 7-9, the Examiner states "[s]imilarly is the case with appellant's statement with regard to no leakage of active agents from true liposomes."

Liposomes are known to be closed, particular structures used as drug delivery vehicles (see page 467 of Szoka and Papahadjopoulos, *supra*). Liposomes are able to retain the entrapped compound for extended periods, as noted on page 500 of Szoka and Papahadjopoulos, *supra*).

4. Finally, the Examiner asserts that Appellant argues that "Marshall's formulations do not have a biologically active agent" (page 3, lines 16-18 of Examiner's Answer). Appellant respectfully clarify that Marshall *et al.* fail to teach a liposome having an entrapped therapeutic agent as described on page 5, lines 16-27 of Appellant's Appeal Brief.

CONCLUSIONS

In view of the foregoing remarks, Appellants submit that the pending claims are in condition for allowance and patentably define over the prior art, and urge the Board to overturn the Examiner's rejections.

Respectfully submitted,

Jacqueline F. Mahoney

Date: Feb. 27, 2004

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